#7

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Youlin Lin
Serial No. 338,382
Filed: January 11, 1982 Group Art Unit 126
For: Chemical Compounds
Examiner: B. Helfin

DECLARATION

I, Ronald M. Hopkins, of 15667 Heathercroft Drive, Chesterfield, Missouri, hereby declare as follows:

1. I graduated from the University of Maryland School of Pharmacy in 1963, obtained a Master of Science degree in Pharmacology from the University of Maryland in 1967 and received by Ph.D. degree in Pharmacology from the University of Maryland in 1970. I have been employed by Mallinckrodt, Inc. since 1970, first as a Research Pharmacologist and then as Senior Research Pharmacologist till 1976, next as Assistant Director of Research in charge of Pharmacology and Toxicology and since 1980 as Associate Director of Research in charge of Pharmacology and Toxicology, Pharmacy and Intravascular Catheter Research. I have completed pharmacological testing on various x-ray contrast media, including nonionic x-ray contrast media, and am familiar with the above-identified patent application.

2. Under my direction, the following experimental compounds have been subjected to varying degrees of toxicity evaluation in animals:

No/Name	Compound
Metriza-mide:	2-[3-Acetamido-2,4,6-triiodo-5-(N-methylacetamido) benzamido]-2-deoxy-D-glucopyranose - U.S. 3,701,771 - Almen et al.
Iopamidol:	N,N'-Bis-[2-hydroxy-1-(hydroxymethyl)ethyl]-5-lactamido-2,4,6-triiodo-isophthalamide - U.S. 4,001,323 - Felder et al. (I)
MP-328	N,N'-Bis-(2,3-dihydroxypropyl)-5-[N-(2-hydroxyethyl)-glycolamido]-2,4,6-trioodo-isophthalamide

No/Name	Compound
C-29	N,N'-Bis-(2,3-dihydroxypropyl)-5-[N-2-hydroxyethyl)-acetamido]-2,4,6-triiodo-isophthalamide - U.S. 4,250,113 - Nordal et al.
Iohexol	N,N'-Bis-(2,3-dihydroxypropyl)-5-[N-2,3,-dihydroxy-propyl)-acetamido]-2,4,6-triiodo-isophthalamide - U.S. 4,250,113 - Nordal et al.
MP-301	N,N'-Bis-(2,3-dihydroxypropyl)-5-N-methylglycolylamido-2,4,6-triiodo-isophthalamide-EPO 26281 - Felder et al. (II)
Iopromide	N-(2,3-Dihydroxypropyl)-N-methyl-N'-(2,3-dihydroxy-propyl)-5-methoxyacetamido-2,4,6-triiodo-isophthalamide - German 2909439 - Speck

In three primary tests designed to predict angiographic and myelographic safety, i.e., acute intravenous (IV) toxicity in mice and acute intracisternal (ICis) toxicities in rats and dogs, results were as follows:

Compound	Mouse I.V. LD_{50} (mg I/kg)	Rat ICis. LD_{50} (mg I/kg)	Dog I.Cis. Neurotoxicity
Metrizamide	12,700	135	Convulsions @ 60 mg I/kg
Iopamidol	22,000	800	Convulsions @ 250 mg I/kg
MP-328	20,000	1,100	Only sedation up to 320 mg I/kg
C-29	15,000	950	Convulsions and death @ 260 mg I/kg
Iohexol	19,000	1,000	Convulsions and death @ 260 mg I/kg
MP-301	20,400	820	Pre-convulsive response @ 240-260 mg I/kg
Iopromide	16,000	125	Pre-convulsive @ 100 and 150 mg I/kg; Convulsions @ 200 mg I/kg

In my opinion, these data demonstrate that

the chemically similar isophthalamide series of compounds is generally less toxic than the established agent metrizamide. Also similar within that series is the generally greater toxicity of iopromide, the only compound with a 5-substituted methoxy group and a N-substituted methyl group. With the exception of MP-328, the remaining contrast media in the series are generally similar with respect to systemic and central nervous system (CNS) toxicity. Of importance was the finding that all except MP-328 caused pre-convulsive or convulsive behavior in dogs at similar intracisternal dose levels below 250 mg I/kg. MP-328, although similar intraveneously, exhibited remarkable CNS safety with the highest LD_{50} value after intracisternal injection in rats and no evidence of significant neurotoxicity in dogs at intracisternal doses up to 320 mg I/kg, the maximum level administered. This was completely unpredictable based on chemical structure relationships.

Although in my opinion a structure-activity relationship is not predictable for MP-328, there would appear to be a correlation for such compounds between safety in animals and safety in humans. For example, metrizamide with relatively low CNS safety in animals has been reported to cause a relatively high incidence of adverse reactions when used as a myelographic agent in humans, ranging from headaches to grand mal epileptogenic seizures (Ref. 1-5). On the other hand, iopamidol is considerably less toxic in animals and is reported to be better tolerated in human myelography (Ref. 6-7). To further support this contention, another myelographic agent, iogulamide, has an animal toxicity profile significantly superior to metrizamide (Ref. 8). In humans, it is also significantly better tolerated during myelographic procedures (Ref. 9). These relationships suggest an excellent clinical safety margin for MP-328, which, based on superior tolerence in animals, could be greater than for other agents. This greater margin of safety is important in many of the diagnostic procedures wherein these compounds are employed since the patients are at greater risk i.e., seriously ill, elderly, or apprehensive and the most benign agent available is the preferred one.

In my opinion, the overall conclusion that may be reached from this information is that MP-328 is a non-ionic contrast medium that exhibits unexpected CNS safety when compared to chemically similar agents and that such safety would be expected to be predictable in humans. The reason for the difference in CNS safety is unclear. It could not be predicted based on chemical structure relationships.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified patent application or any patent issuing thereon.

Ronald M. Hopkins

Ronald M. Hopkins

Dated: 11/4/82

REFERENCES

1. Baker, R.A. et al.: Sequelae of metrizamide myelography in 200 examinations. AJR 130: 499-502, 1978.

2. Gelmers, H.F.: Adverse side effects of metrizamide in myelography. Neuroradiology 18: 119-123, 1979.

3. Kieffer, S.A. et al.: Contrast agents for myelography. Clinical and radiological evaluation of Amipaque and Pantopaque. Radiology 129: 645-705, 1978.

4. Legre, J. et al.: Prevention of adverse reactions to Amipaque in cervical myelography. J. Neuroradiology 8: 353-361, 1981.

5. Sackett, J.F. et al.: Metrizamide - CSF contrast medium. Radiology 123: 779-782, 1977.

6. Hammer, B. et al.: Iopamidol, a new nonionic hydrosoluble contrast medium for neuroradiology. Neuroradiology 19: 119-122, 1980.

7. Leonardi, M. et al.: Myelography with axial tomography and a new contrast medium: iopamidol (B 15,00). J. Neuroradiology 8: 55-62, 1981.

8. Hopkins, R.M. et al.: Iogulamide: A new nonionic intrathecal contrast agent. Presentation at 12th Symposium Neuroradiologicum, Washington, D.C., October 10-16, 1982.

9. Osborn, A.G., et al.: Clinical experience with iogulamide: A new nontoxic myelographic agent. Presentation at 68th Annual RSNA Meeting, Chicago, IL., November 28-December 3, 1982.

A B S T R A C T*

IOGULAMIDE: A NEW NONIONIC INTRATHECAL CONTRAST AGENT

Ronald M. Hopkins, Ph.D.,[1] Anne G. Osborn, M.D.,[2] Max D. Adams, Ph.D.,[1] Robert D. Zimmeramn, M.D.,[3] G. Brooke Hoey, Ph.D.,[1] David A. Norman, M.D.[4]

Iogulamide is a new nonionic contrast agent developed primarily for intrathecal use. Comparative preclinical animal studies demonstrated an acute safety profile significantly superior to that of metrizamide. Improved safety was unrelated to low osmolality. Intrathecally administered iogulamide produced no evidence of epileptogenic activity at concentrations up to 520 mgmI% (260 mgm I/kg). Mild microscopic leptomeningeal inflammatory activity was comparable to that produced by metrizamide. Clinical experience with 11 patients referred for routine water soluble lumbosacral myelography produced technically satisfactory diagnostic studies and no observable adverse side effects. The pharmacokinetics of this new contrast agent will be described and its potential advantages emphasized.

[1] Department of Pharmacology and Toxicology Research, Research and Development Division, Medical Products Group, Mallinckrodt, Inc., St. Louis, MO

[2] Department of Radiology, University of Utah School of Medicine, Salt Lake City, Utah

[3] Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

[4] Department of Radiology, University of California, San Francisco, California

*Presented at the Twelfth Symposium Neuroradiologicum, Washington, D.C., October 10-16, 1982.